Clinical Outcomes of Impending Nasal Skin Necrosis Related to Nose and Nasolabial Fold Augmentation with Hyaluronic Acid Fillers

Zhong-Sheng Sun, M.D.
Guo-Zhang Zhu, M.D., Ph.D.
Hai-Bin Wang, M.D., Ph.D.
Xiang Xu, M.D.
Bing Cai, M.D.
Li Zeng, M.D.
Jin-Qing Yang, M.D.
Sheng-Kang Luo, M.D., Ph.D.

Guangzhou City, People's Republic of China

Background: Although there are several case reports of facial skin ischemia/necrosis caused by hyaluronic acid filler injections, no systematic study of the clinical outcomes of a series of cases with this complication has been reported.
Methods: The authors report a study of 20 consecutive patients who developed impending nasal skin necrosis as a primary concern, after nose and/or nasolabial fold augmentation with hyaluronic acid fillers. The authors retrospectively reviewed the clinical outcomes and the risk factors for this complication using case-control analysis.
Results: Seven patients (35 percent) developed full skin necrosis, and 13 patients (65 percent) recovered fully after combination treatment with hyaluronidase. Although the two groups had similar age, sex, filler injection sites, and treatment for the complication, 85 percent of the patients in the full skin necrosis group were late presenters who did not receive the combination treatment with hyaluronidase within 2 days after the vascular complication first appeared. In contrast, just 15 percent of the patients in the full recovery group were late presenters ($p = 0.004$).
Conclusions: Nose and nasolabial fold augmentations with hyaluronic acid fillers can lead to impending nasal skin necrosis, possibly caused by intravascular embolism and/or extravascular compression. The key for preventing the skin ischemia from progressing to necrosis is to identify and treat the ischemia as early as possible. Early (<2 days) combination treatment with hyaluronidase is associated with the full resolution of the complication. (*Plast. Reconstr. Surg.* 136: 434e, 2015.)
CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, IV.

Hyaluronic acid is widely injected for nose and nasolabial fold augmentations.[1] The vascular complications associated with these procedures include rare (<0.1 percent) soft-tissue necrosis and vision impairment, possibly caused by accidental intravascular filler injection and/or extravascular filler compression.[2–4]

There are multiple case reports regarding impending skin necrosis that developed after nose and nasolabial fold augmentations with hyaluronic acid fillers.[2,5–10] Hirsch et al. reported the first successful management of such a case using hyaluronidase in 2007.[5] Later, Grunebaum et al. reported three similar cases.[6] Four Korean teams recently described seven similar cases.[7–10] However, because each report studied just a few patients, there is little information about the clinical outcomes and the factors that affect the outcome.

In this article, we report a series of 20 consecutive patients with impending nasal skin necrosis that developed after nose and/or nasolabial fold

From the Department of Plastic and Reconstructive Surgery, Guangdong Second Provincial People's Hospital.
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augmentation with hyaluronic acid fillers. Using case-control analysis, we retrospectively reviewed the clinical outcomes of these cases, and identified a risk factor that is associated with a poor clinical outcome.

PATIENTS AND METHODS

We systematically reviewed our medical records from January 1, 2008, to December 31, 2014, to identify all patients who were treated at our center for vascular complications associated with facial hyaluronic acid filler injections. In each case, we carefully reviewed the demographics, medical history, prior filler injections, photographs, imaging reports, and laboratory test results.

The statistical analysis was performed using SPSS software version 13.0 (SPSS, Inc., Chicago, Ill.). The distribution of ages was examined using the Kolmogorov-Smirnov test; the ages were expressed as mean ± SD and analyzed using the *t* test. The sex, filler injection sites, and clinical outcomes of the patients were expressed as frequencies, and analyzed using Fisher's exact test. Differences are considered statistically significant for values of $p < 0.05$.

RESULTS

Our retrospective review of the medical records from 2008 to 2014 identified a series of 20 consecutive referral patients with impending nasal skin necrosis associated with nose and/or nasolabial fold augmentation with only hyaluronic acid fillers (Table 1).

The demographic profiles and initial presentations of the 20 patients were fairly homogenous. Most patients (90 percent) were women in their twenties or thirties. Most patients (95 percent) developed pain, erythema, and swelling as the initial signs of a vascular complication within 1 day after the filler injections. All patients presented with impending nasal skin necrosis as a primary concern. The skin lesions fall into three categories: (1) five patients with just nasolabial fold augmentation presented with reticulated skin erythema on the nose and nasolabial fold, with lip involvement in two cases (Fig. 1, *left*); (2) seven nose augmentation patients and one combined nose–nasolabial fold augmentation patient presented with reticulated nasal skin discoloration, with glabella and forehead involvement in four cases (Fig. 2, *left*); (3) the remaining seven patients had just nose augmentation, and presented with localized impending nasal skin necrosis (Fig. 3, *left*), with additional pustules in three cases. (**See Figure, Supplemental Digital Content 1,** which shows the initial presentation of additional representative early presenters who recovered fully from the impending skin necrosis associated with hyaluronic acid filler injection. In patient 11, nose erythema and pustules developed after nose augmentation. In patient 12, reticulated pinkish erythema on the

Table 1. Profiles of the 20 Consecutive Patients with Impending Nasal Skin Necrosis

Patient	Sex	Age (yr)	Injection Site*	Skin Complication	Mechanism†	Treatment‡	Enzyme§	Outcome
1	F	24	Nose	Nose	Pressure	7 days	No	Skin necrosis
2	F	22	Nose	Nose, NLF	Embolism	7 days	Yes	Skin necrosis
3	F	24	Nose	Nose	Pressure	4 days	Yes	Skin necrosis
4	F	28	Nose	Nose, NLF, glabella, forehead	Embolism	1 day	Yes	Skin necrosis
5	F	25	NLF	Nose, NLF, lip	Embolism	3 hr	Yes	Full recovery
6	F	25	Nose	Nose	Pressure	1 days	Yes	Full recovery
7	F	38	Nose	Nose, glabella, forehead	Embolism	1 day	Yes	Full recovery
8	F	24	Nose	Nose, NLF, glabella, forehead	Embolism	9 days	No	Skin necrosis
9	F	25	Nose	Nose	Embolism	2 days	Yes	Full recovery
10	F	52	NLF	Nose, NLF	Embolism	1 hr	Yes	Full recovery
11	M	21	Nose	Nose	Pressure	2 days	Yes	Full recovery
12	F	22	Nose, NLF	Nose, NLF, glabella, forehead	Embolism	0 hr	Yes	Full recovery
13	F	31	Nose	Nose	Pressure	2 days	Yes	Full recovery
14	F	21	Nose	Nose, glabella, forehead	Embolism	5 days	Yes	Full recovery
15	F	35	NLF	Nose, NLF	Embolism	1 day	Yes	Full recovery
16	F	39	NLF	Nose, NLF, lip	Embolism	3 days	Yes	Full recovery
17	F	33	NLF	Nose, NLF, lip	Embolism	2 days	Yes	Full recovery
18	F	34	Nose	Nose	Pressure	5 days	Yes	Skin necrosis
19	F	26	Nose	Nose	Pressure	2.5 days	Yes	Skin necrosis
20	F	37	Nose	Nose, NLF	Embolism	1 day	Yes	Full recovery

F, female; M, male; NLF, nasolabial fold.
*Filler injection sites.
†Proposed primary mechanism of impending skin necrosis. Pressure, pressure necrosis; Embolism, intravascular filler embolization.
‡The time from skin complication manifestation to receiving proper treatment.
§Hyaluronidase treatment.

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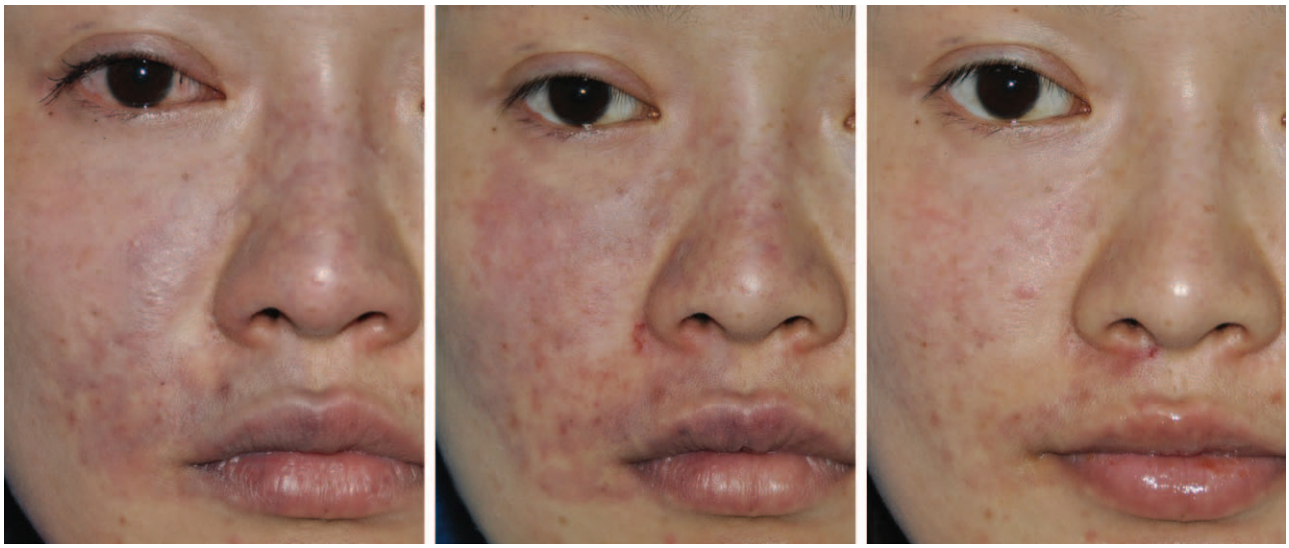

Fig. 1. Patient 5 presented early with bluish purple skin erythema on the nose, right nasolabial fold, and upper lip (*left*), which significantly diminished 1 day after the combination treatment with hyaluronidase (*center*), and almost subsided 5 days after treatment (*right*).

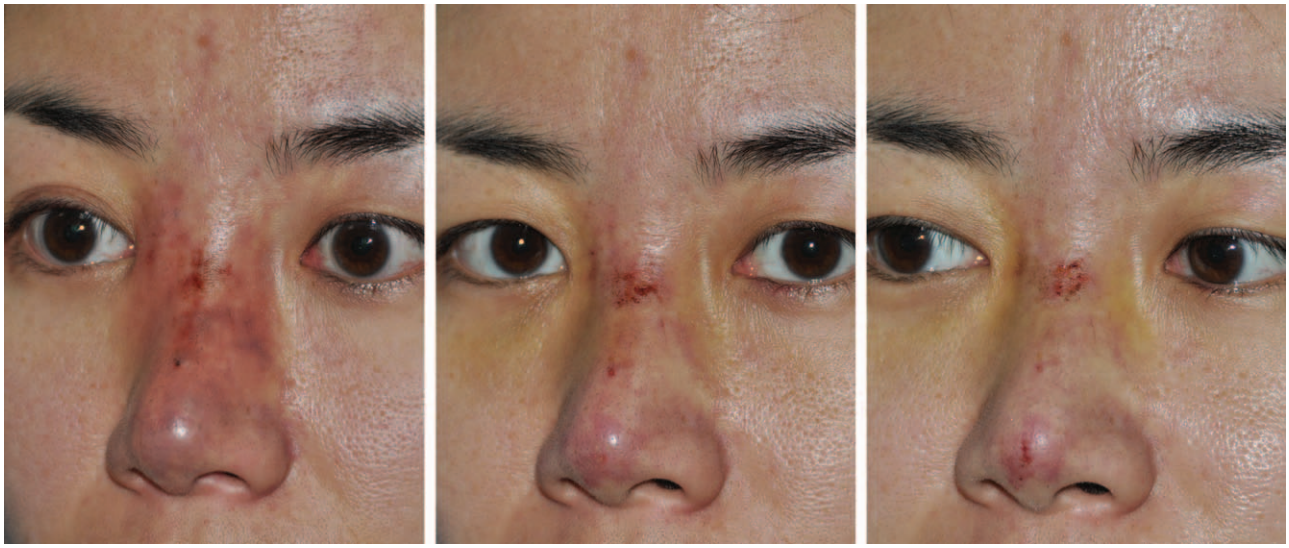

Fig. 2. Patient 7 presented early with reticulated pinkish purple discoloration on the nose, glabella, and forehead (*left*), which dramatically improved 2 days after the combination treatment with hyaluronidase (*center*), and almost subsided 4 days after the treatment (*right*).

nose, nasolabial fold, glabella, and forehead developed after combined nose–nasolabial fold augmentation. In patient 13, nasal tip erythema and pustules developed after nose augmentation. In patient 15, reticulated erythema and pustules on the nose and right nasolabial fold developed after nasolabial fold augmentation. In patient 17, reticulated erythema on the nose, right nasolabial fold, and upper lip developed after nasolabial fold augmentation. In patient 20, reticulated erythema on the nose and left nasolabial fold developed after nose augmentation, ***http://links.lww.com/PRS/B405***.)

All patients, except patients 1 and 8, were managed by our four attending plastic surgeons, using the same combination treatment protocol, which included an injection of ovine testicular hyaluronidase (Shanghai First Biochemical Pharmaceuticals Corp., Shanghai, People's Republic of China; equivalent to Vitrase in North America) into the patient's soft tissues with hyaluronic acid fillers and those with impeding necrosis; antibiotics for infection prevention and control; and tanshinone, papaverine, topical magnesium sulfate, infrared irradiation, and hyperbaric oxygen to improve

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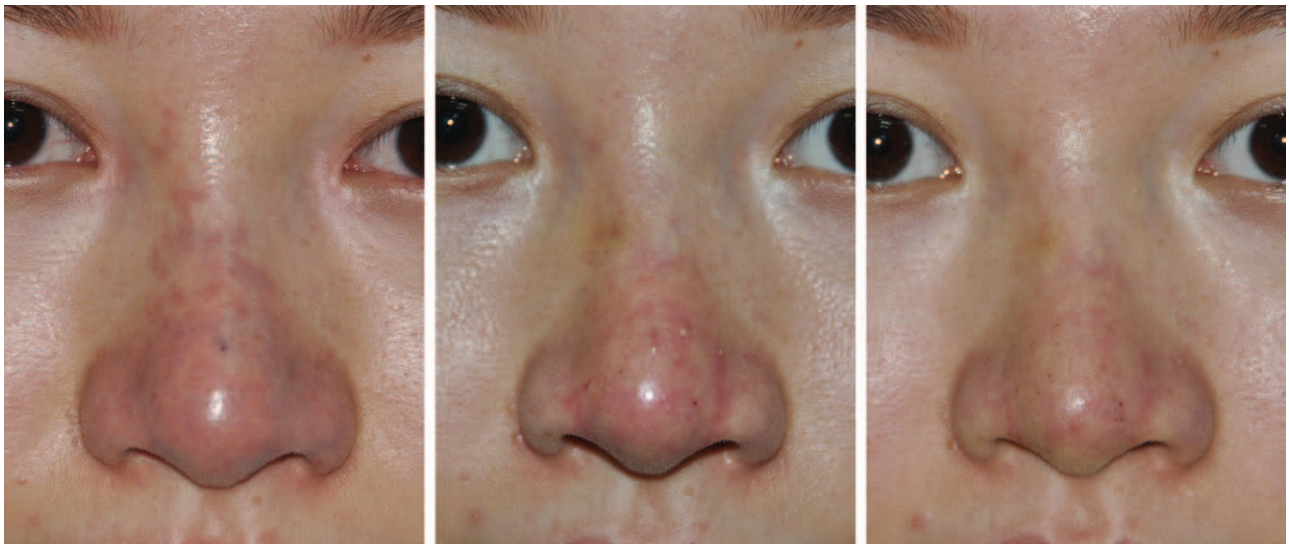

Fig. 3. Patient 6 presented early with homogenous erythema on the nasal tip (*left*), which dramatically improved 2 days after the combination treatment with hyaluronidase (*center*), and almost disappeared 4 days after treatment (*right*).

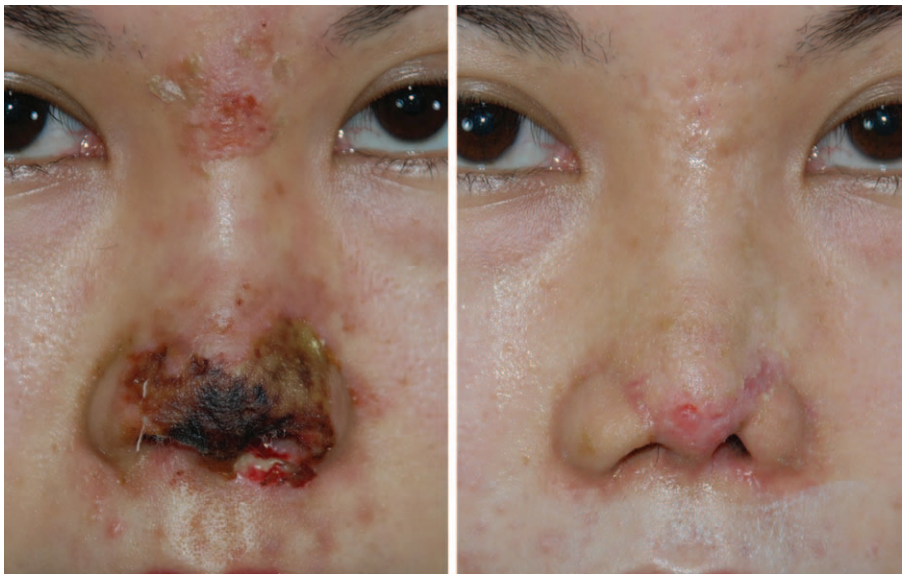

Fig. 4. Patient 1 presented very late with a necrotic nasal tip covered by eschar (*left*), which progressed into significant tissue defects 1 month after conservative wound care without hyaluronidase (*right*).

tissue perfusion and oxygenation. Patients were also given aspirin, unless contraindicated.

After treatment, 13 patients (65 percent) recovered fully (Figs. 1 through 3), and the remaining seven patients (35 percent) developed full skin necrosis and scar formation (Figs. 4 through 7). Although the two groups had similar age, sex, and filler injection sites (Table 2), 85 percent of the patients in the full skin necrosis group did not receive the combination treatment with hyaluronidase within 2 days after the vascular complication first manifested (late presenters). In contrast, just 15 percent of the patients in the full recovery group were late presenters ($p = 0.004$).

Eleven early and two late presenters recovered fully. At the initiation of treatment, they all had fairly fresh skin ischemia (Figs. 1 through 3, *left*). Following the combination treatment with hyaluronidase, the skin erythema typically reduced dramatically within 2 days (Figs. 1 through 3, *center*), and almost subsided within 4 to 5 days (Figs. 1 through 3, *right*).

Six late presenters and one early presenter eventually developed full skin necrosis. Four very

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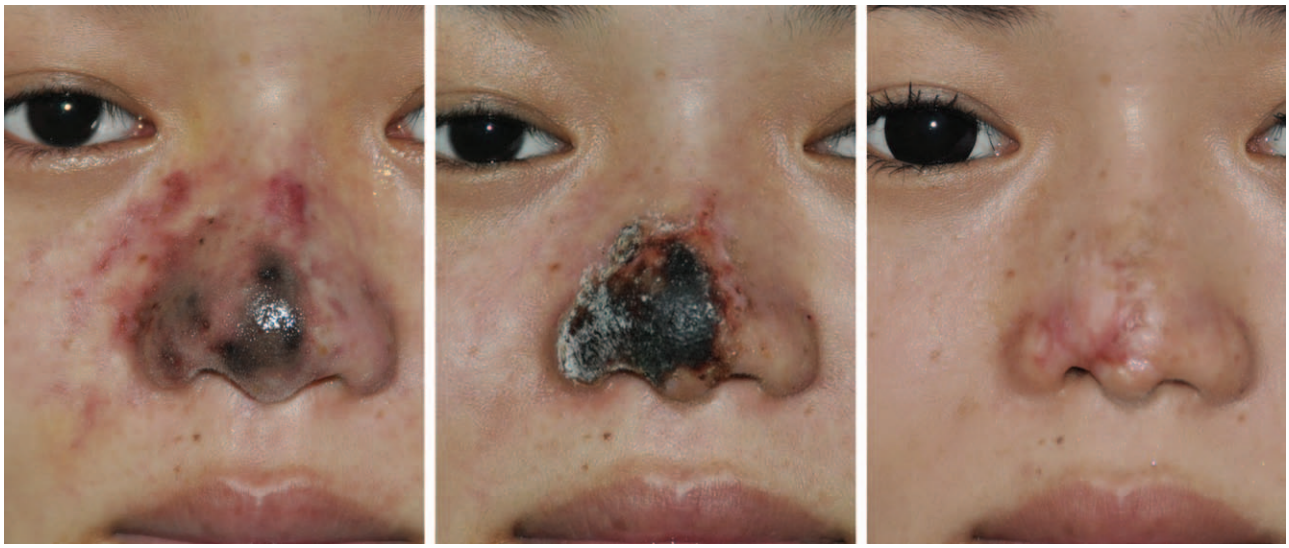

Fig. 5. Patient 2 presented very late with reticulated erythema on the nose and right nasolabial fold, and with anthracosis on the tip and right ala (*left*), which progressed into eschar 6 days after the combination treatment with hyaluronidase, although the surrounding erythema subsided (*center*). Large tip and alar tissue defects were observed at 2-month follow-up (*right*).

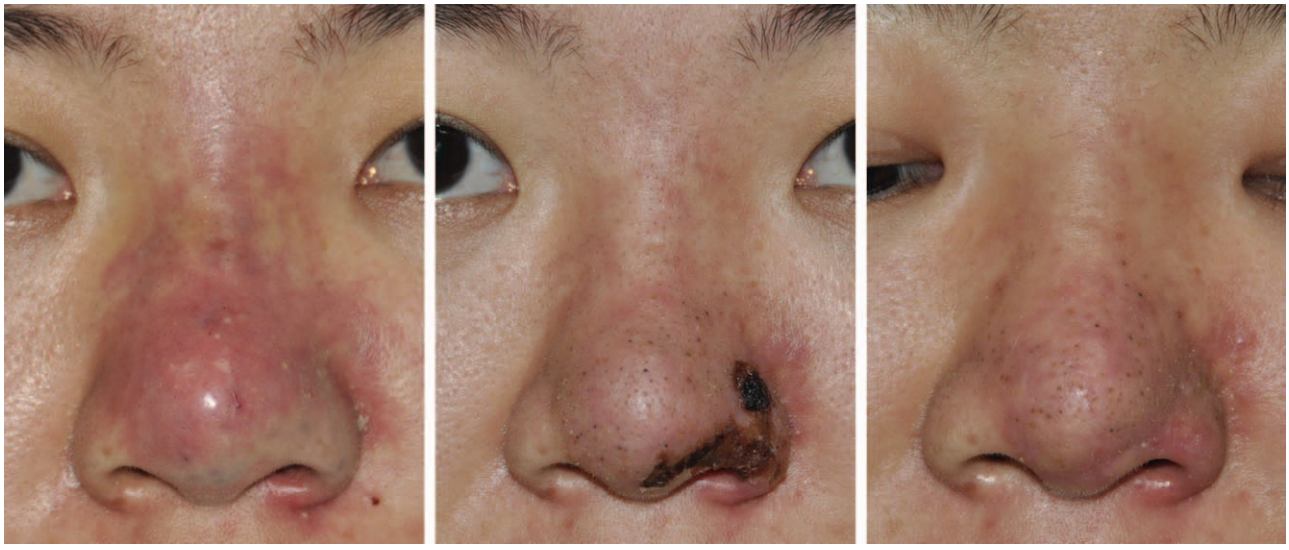

Fig. 6. Patient 19 presented late with nose erythema and grayish discoloration on the tip and left alar rim (*left*), which progressed into eschar 9 days after combination treatment with hyaluronidase (*center*), and into a visible scar at 3-week follow-up (*right*).

late presenters had developed necrotic nasal skin islands with eschar (Fig. 4, *left*) or anthracosis (Fig. 5, *left*), and two late presenters had developed poorly perfused skin islands with grayish discoloration (Fig. 6, *left*) at the time of treatment. This type of skin island was also observed in one early presenter, whose nasal tip and alar skin erythema quickly deteriorated into dusky purple or pale discoloration (Fig. 7, *left*). All skin islands with very poor perfusion progressed into full skin necrosis within several days, although the surrounding erythematic skin recovered (Figs. 5 through 7, *center*). At the final follow-up, two patients developed mild but visible scars (Fig. 6, *right*), and the remaining five patients developed significant tissue defects (Figs. 4 and 5, *right*), including one patient with severe scar contracture and vestibule deformity (Fig. 7, *right*).

DISCUSSION

Nose and nasolabial fold augmentations with hyaluronic acid filler are popular and safe cosmetic procedures, and related vascular complications are

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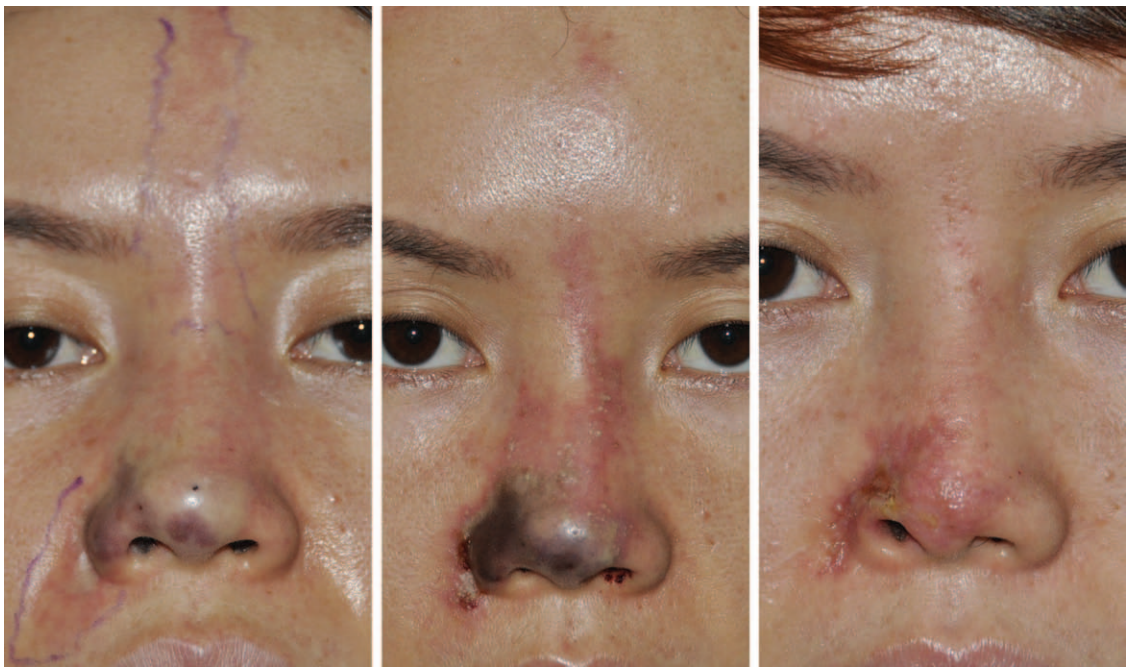

Fig. 7. Patient 4 presented early with reticulated erythema on the dorsum, glabella, forehead and right nasolabial fold (circled with *blue lines*) and with dark purple and pale skin islands on the tip and right ala (*left*), which progressed into eschar 2 days after the combination treatment with hyaluronidase (*center*), and into severe scar contracture and right vestibule deformity at 1-month follow-up (*right*).

Table 2. Case-Control Analysis of Late Presentation as a Potential Risk Factor for Skin Necrosis*

Factors	Full Skin Necrosis ($n = 7$)	Full Recovery ($n = 13$)	p
Mean age ± SD, yr	26.0 ± 4.0	31.1 ± 9.1	0.182 ($t = 1.389$)
Sex, no.			
Male	0	1	
Female	7	12	>0.999
Nose augmentation, no.	7	8	
NLF augmentation, no.	0	5	0.114
Early presenter, no. (%)	1 (15)	11 (85)	
Late presenter, no. (%)	6 (85)	2 (15)	0.004

NLF, nasolabial fold.
*One patient had a combined nose-NLF augmentation but was treated in the statistical analysis as if she had only nose augmentation, because the nose was the main site of filler injection.

very rare.[1–4] A single center typically gets to treat only a few cases, and therefore the correlation between the outcome and the time of therapy initiation has not been well studied.[2] As a major plastic surgery referral and training center in southern China, we treated a series of 20 consecutive patients with impending nasal skin necrosis that developed after nose and/or nasolabial fold augmentations using only hyaluronic acid fillers. By using case-control analysis, we conclude that early treatment is associated with significantly better outcomes.

Hyaluronic acid filler may cause impending skin necrosis through microcirculatory embolism by the filler particles accidentally injected into the vessels that nourish the skin.[2,8,11] Because of the sudden disruption of the vascular supply, patients often develop striking pain and characteristic reticulated erythema in the distribution of the occluded vessels.[5–7,9] If the intravascular embolism is related to nasolabial fold augmentation, the areas of reticulated erythema are found at the nasolabial fold, nose, and lip (Fig. 1, *left* and **Supplemental Digital Content 1, *http://links.lww.com/PRS/B405***), which are nourished by facial artery branches.[5,7] Because the alar plexus is supplied mainly by the lateral nasal artery and its alar branches, with little collateral circulation,[12] the ala is particularly prone to developing ischemia/necrosis. This trend has been reported in the literature[6,8,11] and demonstrated in our series.

If the intravascular embolism is related to nose augmentation, the areas of reticulated erythema are located on the nose, and sometimes also on the nasolabial fold, glabella, and forehead (Figs. 2 and 7, *left* and **Supplemental Digital Content 1, *http://links.lww.com/PRS/B405***),[6,9] whose vascular supplies have extensive anastomoses with the nasal vessels.[12] Because the blood supply of the nasal tip depends mainly on the lateral

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nasal artery, the tip is particularly vulnerable to skin necrosis if this artery is embolized by hyaluronic acid particles. In our series, 50 percent of the impending skin necrosis associated with nose augmentation appears to be caused by this mechanism (Table 1).

Hyaluronic acid filler may also cause impending skin necrosis by externally compressing the vessels that nourish the skin.[2] In nose augmentation, this mechanism is known as pressure necrosis.[13] Nasal skin, especially the dense tip and alar skin envelope, is not quite distensible. Excessive subdermal (particularly intradermal) filler injection can lead to subdermal plexus compression and compromised skin perfusion. The hydrophilic nature of hyaluronic acid can increase the likelihood of subdermal congestion. The skin lesion is mainly located at the areas where the filler has been placed (Figs. 3, 4, and 6, *left*; **Supplemental Digital Content 1,** ***http://links.lww.com/PRS/B405***).[10] In our series, 50 percent of the impending skin necrosis related to nose augmentation seems to have been caused by this mechanism, with tip and alar necrosis as the primary concern (Table 1).

To prevent skin ischemia in augmentation of the nose and nasolabial fold using hyaluronic acid filler, physicians should practice safe injection techniques.[2,14] Filler should be injected slowly and gently, preferably using a small syringe with a larger profile blunt cannula to reduce the risk of intravascular filler injection, or with a smaller bore needle to minimize tissue injury. Epinephrine may be added to the filler for vessel constriction. Nose, nasolabial fold, and glabella are known danger zones, where it is essential to aspirate to verify a negative flashback before making any filler injection.

To minimize intravascular hyaluronic acid injection in nose augmentation, the filler should be placed along the midline of the radix, dorsum, supratip, and nasal spine, and below the subcutaneous and musculoaponeurotic system layer, in which the major vasculature of the nasal skin is located.[13] To prevent pressure ischemia in nonsurgical rhinoplasty, especially Asian rhinoplasty,[15] the filler injected into the nose (particularly the tip) should be conservative. For patients with a history of nose surgery or trauma, the nose augmentation should be approached with even more caution and less filler in one session.[13,15]

To prevent hyaluronic acid–related skin ischemia from developing into full skin necrosis, the key is to identify the complication as early as possible. During filler injection, physicians should be alert to signs of potential skin ischemia, such as abnormal pain, blanching, erythema, swelling, and poor capillary refill. If impending skin necrosis is suspected, the filler injection should be discontinued immediately, and massaging and hyaluronidase treatment should be initiated. Patients should be educated to call back if they experience the symptoms and signs of a delayed vascular complication.[16]

In the event of hyaluronic acid–related impending skin necrosis, the most critical treatment is hyaluronidase injection to hydrolyze the injected hyaluronic acid and restore skin perfusion.[2,5] It is recommended that this treatment be started as early as possible.[7,9] Our study clearly demonstrates that early (<2 days) combination treatment with hyaluronidase is associated with full recovery from the complication (Table 2). If patients are treated within 2 days, it is more likely that the skin ischemia is fresh and can readily resolve within 1 week after this treatment, without developing any sequelae (Figs. 1 through 3). If treatment is delayed for more than 2 days, patients are at greater risk for developing very badly perfused skin islands (Figs. 4 through 7), which cannot be salvaged by this treatment and can progress to full skin necrosis with tissue defect.

To treat a patient with hyaluronic acid–related impending skin necrosis, we typically dissolve 150 U.S. Pharmacopeia units of ovine testicular hyaluronidase in 1.0 ml of saline, and inject the solution into the soft tissues that may contain hyaluronic acid and those with impending skin necrosis. The tissue with filler is generally stiffer than the surrounding normal tissue. We massage the tissue as we inject the enzyme, and monitor tissue tension and stiffness by palpation. This typically takes approximately 10 minutes, during which time fluid flows out through the needle holes and the tissue gradually becomes softer and more relaxed. In our experience, 150 U.S. Pharmacopeia units of hyaluronidase is sufficient to treat most patients. In a more severe case with excessive filler placement and tissue tension, we may also decompress the soft tissues using an empty syringe to aspirate the hyaluronic acid, and treat the tissues with up to 300 U.S. Pharmacopeia units of hyaluronidase in 2.0 ml of saline. After enzyme treatment, we give patients other supportive treatments (aspirin, topical magnesium sulfate, intravenous tanshinone, intramuscular papaverine, infrared irradiation, and hyperbaric oxygen) that also appear to be beneficial. Nitroglycerin paste is also commonly used by other physicians for the treatment of this condition.[2]

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Our study has two limitations. First, our data came from only one referral center in southern China, where approximately two-thirds of the patients seek hyaluronic acid filler injections for facial contouring (unpublished survey result), rather than for the rejuvenation of soft tissue aging as is practiced in the Western world.[1] In addition, our patients were all referrals, so we did not have access to the primary data to study the correlation between the filler dose and outcome.

CONCLUSIONS

Nose and nasolabial fold augmentation with hyaluronic acid fillers can lead to impending nasal skin necrosis, possibly caused by intravascular embolism and/or extravascular compression. The key to preventing the skin ischemia from progressing into necrosis is to identify and treat the ischemia as early as possible. Early (<2 days) combination treatment with hyaluronidase is associated with full resolution of the complication.

Sheng-Kang Luo, M.D., Ph.D.
Department of Plastic and Reconstructive Surgery
Guangdong Second Provincial People's Hospital
466 Middle Xin Gang Road
Guangdong Province
Guangzhou City 510317, People's Republic of China
gdprs@sina.com

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PATIENT CONSENT

Patients provided written consent for the use of their images.

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